EPIDEMIC MODELS

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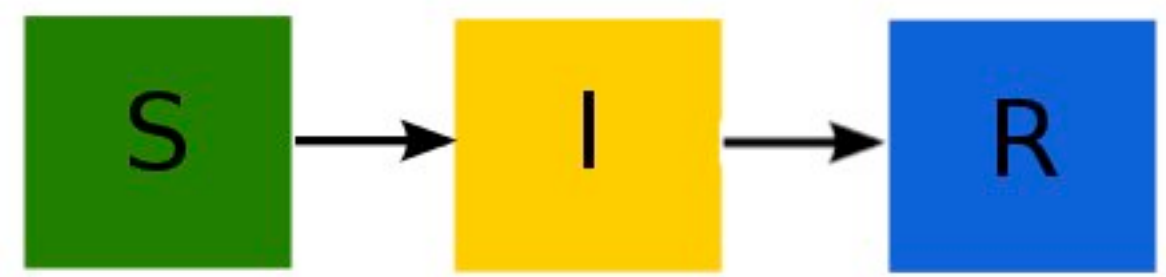
Epidemic models =>
- essential features of spread of infectious disease
- (approximate) quantification
- in silico experiments
= essentially mathematical/probabilistic/computeristic language
= for applications, essential to fit models and reality = statistics...

BASIC SIR MODEL

S(usceptible) -> I(nfective) -> R(emoved)



Variants: SEIR, SIS, ... + diseases I will not talk about such as parasites, STD, ...

Mathematical meaning of rate (in our case...) = # events/time unit

Individual rate of S -> I = FOI (force of infection)

Individual rate of I -> R = removal rate (recovery/immunity, death)

Simplest representation of SIR

S, I, R = numbers of such individuals in a population = N
(closed vs demographic...)

rate of S -> I = S x FOI = S x (contact rate of infectives x 1/N x probability that contact transmits x number of infectives) = $\beta SI/N$

rate of I -> R = I x removal rate = γI (γ = 1/average duration of I-period)

Let us consider S(t), I(t) and R(t) as functions of time (t=0 "start of epidemic"), then rates of change can be interpreted as derivatives and we can then write down a "system of ODEs":

$$S'(t) = -\beta S(t)I(t)/N$$
$$I'(t) = \beta S(t)I(t)/N - \gamma I(t)$$
$$R'(t) = \gamma I(t)$$

$$S(0) = N - I_0$$
$$I(0) = I_0$$
$$R(0) = 0$$

A mathematician can deduce various properties of these equations,
some "obvious", some less...

Epidemic threshold theorem

There is a number $R_0 = \beta/\gamma$ = average number of secondary cases to a primary case when all contacts are susceptible (beginning of epidemic) such that
$R_0 \leq 1$ => no large epidemic can arise,
$R_0 > 1$ => large epidemic arises (however, see stochastic interpretation later...)

It is officially called "the basic reproduction number of the disease".
Dependence on social structure and community size?

Intervention corollarium

If R_0 can be reduced by a proportion $1-1/R_0$ or more, resulting in $R_{eff} \leq 1$, there will be no epidemic

Initial exponential growth

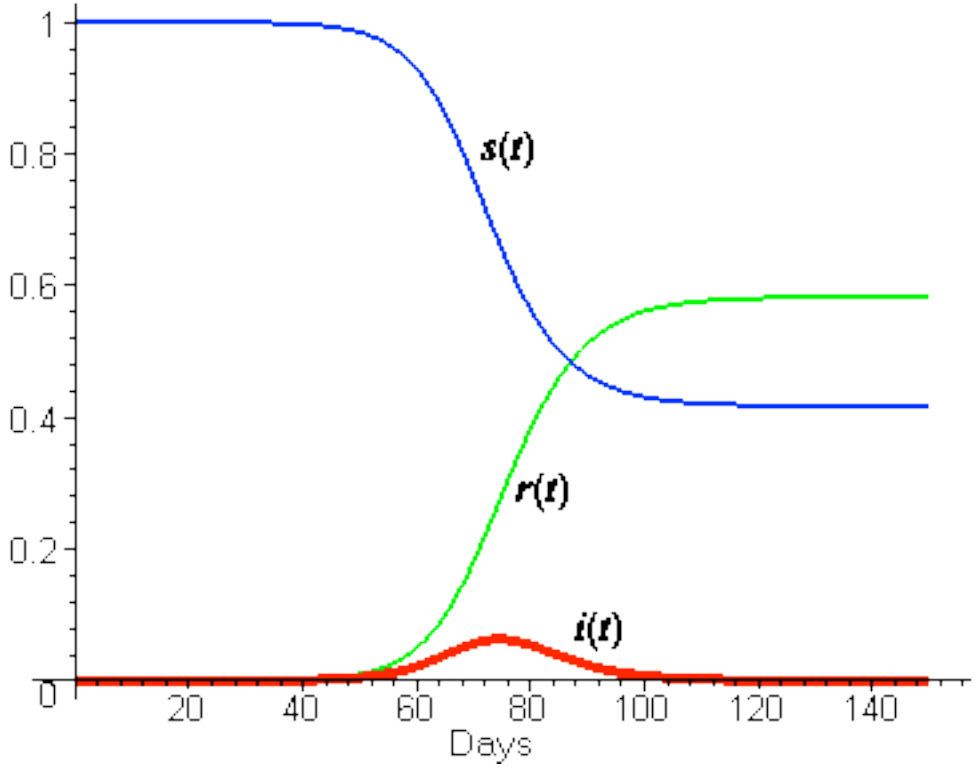
If an epidemic takes off, it grows exponentially to start with, then reaches a peak, then declines until it dies out...

Final size equation

The epidemic will, if left undisturbed, eventually infect a proportion τ of the population and τ is the largest positive solution of

$$\tau = 1 - e^{-R_0 \tau}$$

Ex. R0 = 1.5, i_0 very small...



Notice the "strange" visual effect of exponential increase (doubling time)...

Some modellers prefer **probabilistic** formulations...

Contacts and recovery occur at random, but following given distributions and averages... => more individual oriented view...

In the basic SIR model, the only relevant difference is that, when $R_0 > 1$, large epidemics may occur with a certain probability, but the outbreak may also die out by chance...

However, the probabilistic perspective makes it easier to connect what we think happens with what can be observed...

Let us look at an interesting quantity: **generation time** of a disease...

GT = (average) time between the infection of an infectee (secondary case) and the infection of the infector (primary case)

Generation time in analogy with demography...

The generation may vary according to the GT distribution g(t) which appears in a famous equation (the Lotka-Volterra equation):

$$\int_0^\infty R_0 g(t) e^{-rt}\, dt = 1$$

which connects the reproductive number R_0 , the GT distribution and the Malthusian parameter r...

However, closer (probabilistic) analysis of the concept shows:

- the distribution (and average) depend on how GT is measured:
forwards ≠ backwards
- backwards = contact tracing gives shorter times in the initial phase...
- forwards almost stable, but shorter around peak...
- usually, infection is not seen, but symptoms are...

Time between appearance of symptoms in infector-infectee is called **serial time** and should on average have same length as GT, but, unless symtoms appear exactly when infectivity starts, has a distribution with larger variance, which matters in many calculations...

A little interlude about: averages are not enough...

A painter paints square placards.
Half of the placards have sidelength L = 1m, the other half L= 3m
=> average L = 2m
However, quantity of paint needed depends on surface area...
Surface of square = L^2

Thus, average surface = $(2m)^2$ = 4 m^2, right...?

WRONG !!

Average surface = $1/2 \times (1m)^2 + 1/2\ (3m)^2 = 1/2(1+9)\ m^2 = 5\ m^2$...

Realism...

Much work has been done on more "realistic" models...

- constant infection rates -> infectivity profiles
- constant recovery rates -> general distributions of IP
- homogeneous mixing -> multitype populations, structured populations (households), network models...
- demographic realism (births, deaths, immigration, age structure...)

but much remains to investigate...

Parametrizing infectious contacts between age groups

The POLYMOD study, EU project FP6 2004-2008

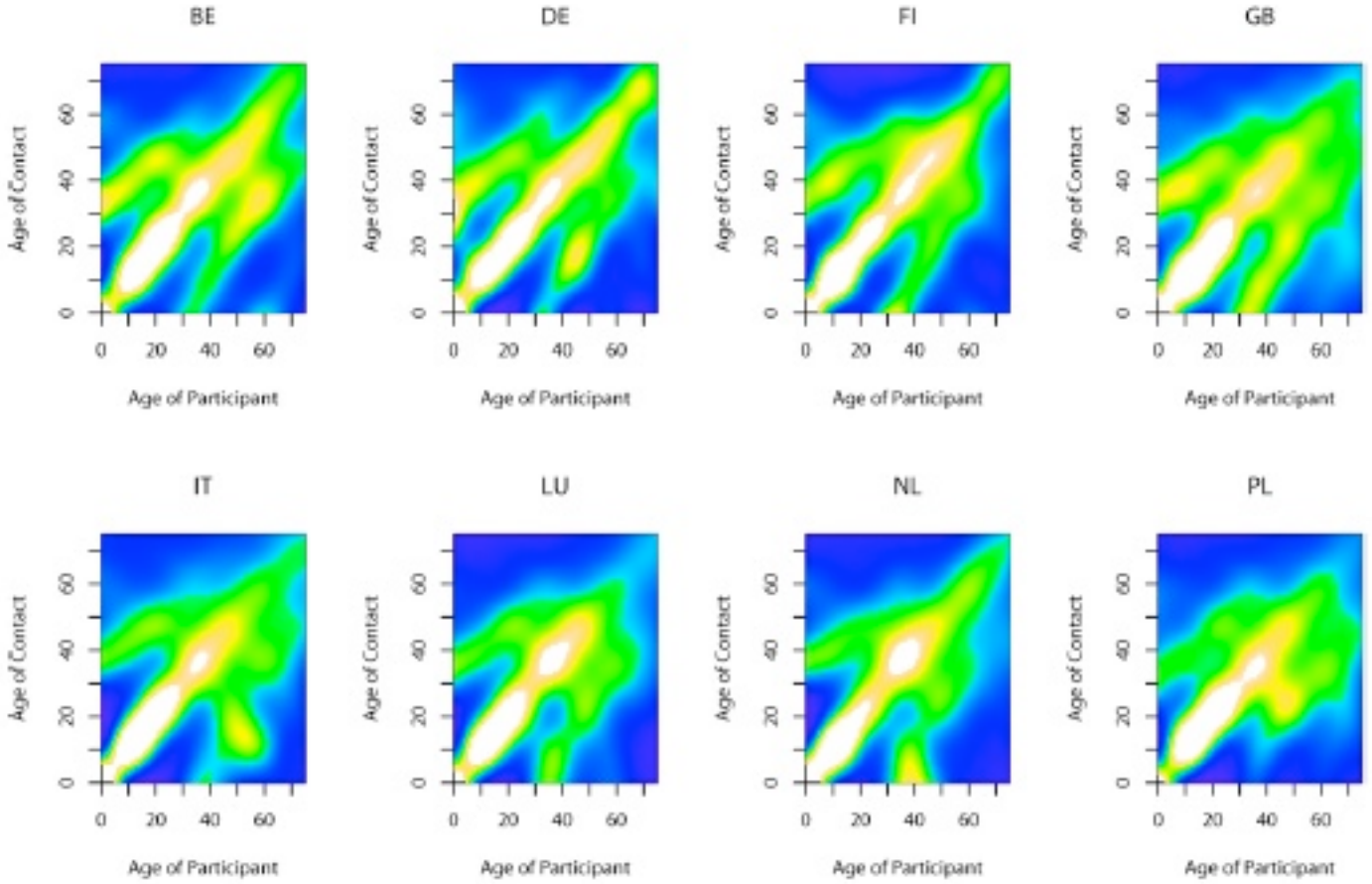
Previous approach Anderson & May (1991) Infectious Diseases of humans: dynamics and control -> WAIFW matrix

Structured for mathematical convenience...

The POLYMOD study: social contact hypotheses -> infectious contacts are proportional to social contacts...

- need to define social contacts...
- diary based population based study in 8 European countries
- evaluation of the contact matrix = average number of contacts between person of one age group with persons of another age group... (interesting balance , aggregation and norming problems...)

Result: the general pattern is the same in all countries, but the levels are not
-> people mix preferentially with same age groups + parents and grandparents...


BE
DE
FI
GB
IT
LU
NL
PL
Age of Contact
Age of Participant
0
20
40
60

Evaluating interventions against A(H1N1) in 2009 in Norway

The main outbreak of influenza A(H1N1) started in week 40 in 2009 in Norway, peaked in week 45 and lasted until the start of 2010...
The epidemic could be followed in relative terms, as percentage of ILI on all reported disease by a sentinel system, and purchases of antivirals and vaccinations could be followed over time thanks to official registers.
Antivirals were mainly sold between weeks 41 and 53 and vaccination started in week 43 and essentially ended in week 51, having reached a population coverage of about 40%...

Question: how much did interventions change the course of the epidemic?

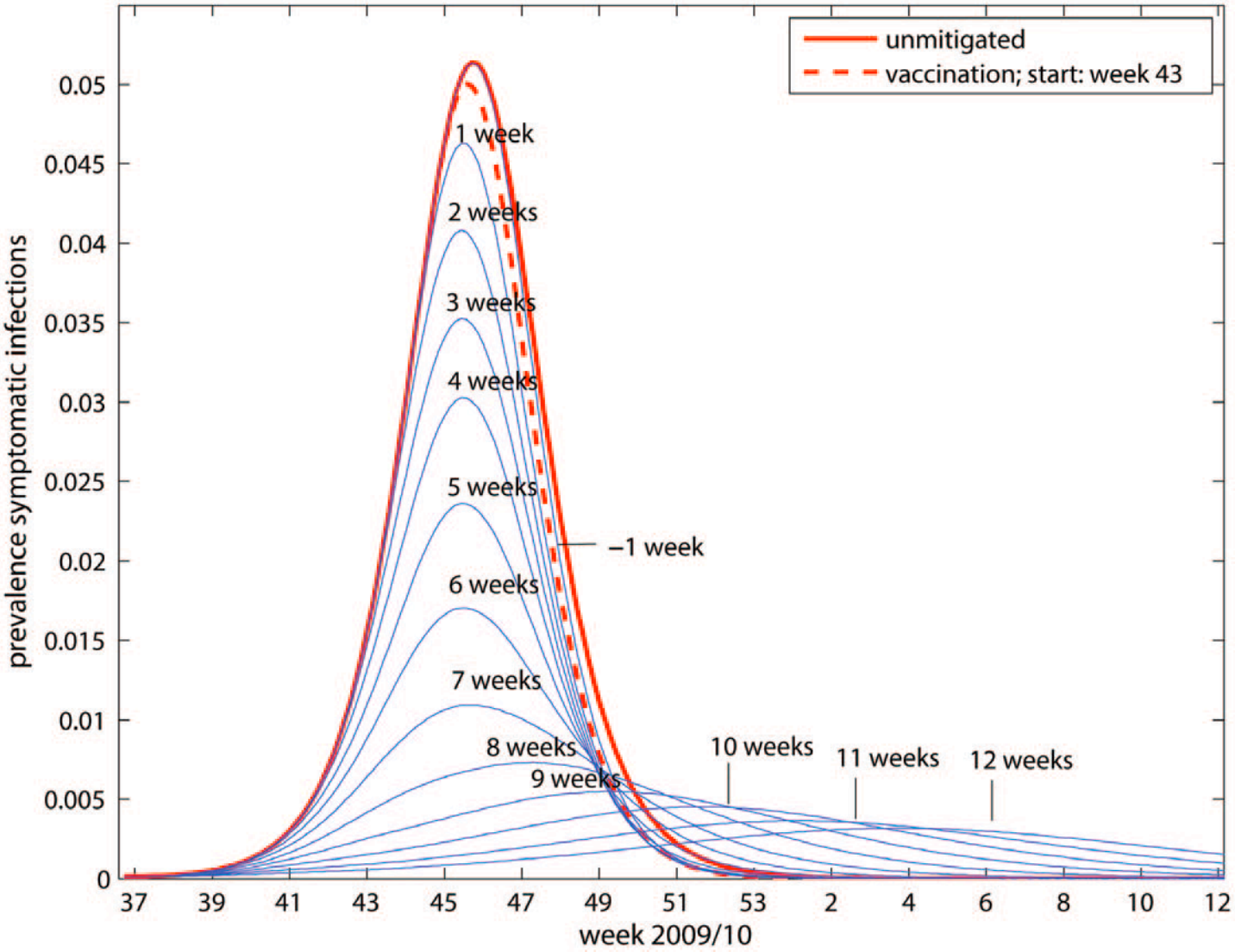
Strategy: an age dependent model, taking known and estimated effects of interventions into account, was fitted to data, in order to estimate the parameters of the disease.

Once parameters were known, a counterfactual epidemic without interventions could be simulated and the difference described...

In conclusion, the interventions seemed to have decreased the spread by 11-12% in relative terms (from 32-33% of the population to 29-30%) and most of this effect was due to vaccination...

The effective reproduction number (taking partial immunity in some adults into account) was 1.35 and a vaccination coverage of 40% should have reduced this to 0.80... However, vaccination came too late to have a large effect...

However, the simulations also showed the great importance of timing of interventions. The following graph shows what would have happened if the same vaccination effort had started earlier than what actually happened...


unmitigated
vaccination; start: week 43
1 week
2 weeks
3 weeks
4 weeks
5 weeks
−1 week
6 weeks
7 weeks
8 weeks
9 weeks
10 weeks
11 weeks
12 weeks
prevalence symptomatic infections
0
0.005
0.01
0.015
0.02
0.025
0.03
0.035
0.04
0.045
0.05
37
39
41
43
45
47
49
51
53
2
4
6
8
10
12
week 2009/10

Boosting immunity or "the last contact"

Varicella is a childhood disease that gives permanent immunity to the disease, but the virus remains dormant in dorsal ganglia and may reemerge at later age giving rise to Hepes Zoster...

It has been hypothesized that contacts with varicella-infectious individuals may boost immune defenses against the virus and thus prevent HZ.

However, although models for infectious contact rates (FOI) are continuous in time, contacts as such are discrete events. Thus one can talk about the last contact in life, whereafter immune defenses would no more be boosted...

Can something be said about the likely age of this "last contact"?

The Force of Infection rate is usually used to represent the risk of having the first infectious contact with the disease at various ages, but assuming that having had the disease (usually during childhood) does not change this risk at higher ages, one may use the same rate function also for later contacts with the virus...

Assuming that contacts will occur with the given rate function according to a Poisson process (a typical probabilistic object...), one can then calculate that the time of last contact has a probability density function of the form

$$f_L(a) = \frac{1}{P(C \geq 1)} \int_a^{\infty} \lambda(a) \cdot e^{-(\Lambda(t)-\Lambda(a))} f_T(t)\, dt$$

where C is the number of lifetime contacts, λ is the force of infection , Λ the cumulated force of infection and f_T the density of life length...

The problem now becomes to correctly estimate the force of infection λ(a) at different ages...

This can be done by considering seroprevalence studies, i.e. studies of the proportion of the population at various ages that has already had the disease (by finding antibodies against the virus in serum) and using the relation (which requires the assumption of stable population and infection dynamics over time) between probability P(a) of having had the disease before age a and the FOI of the disease

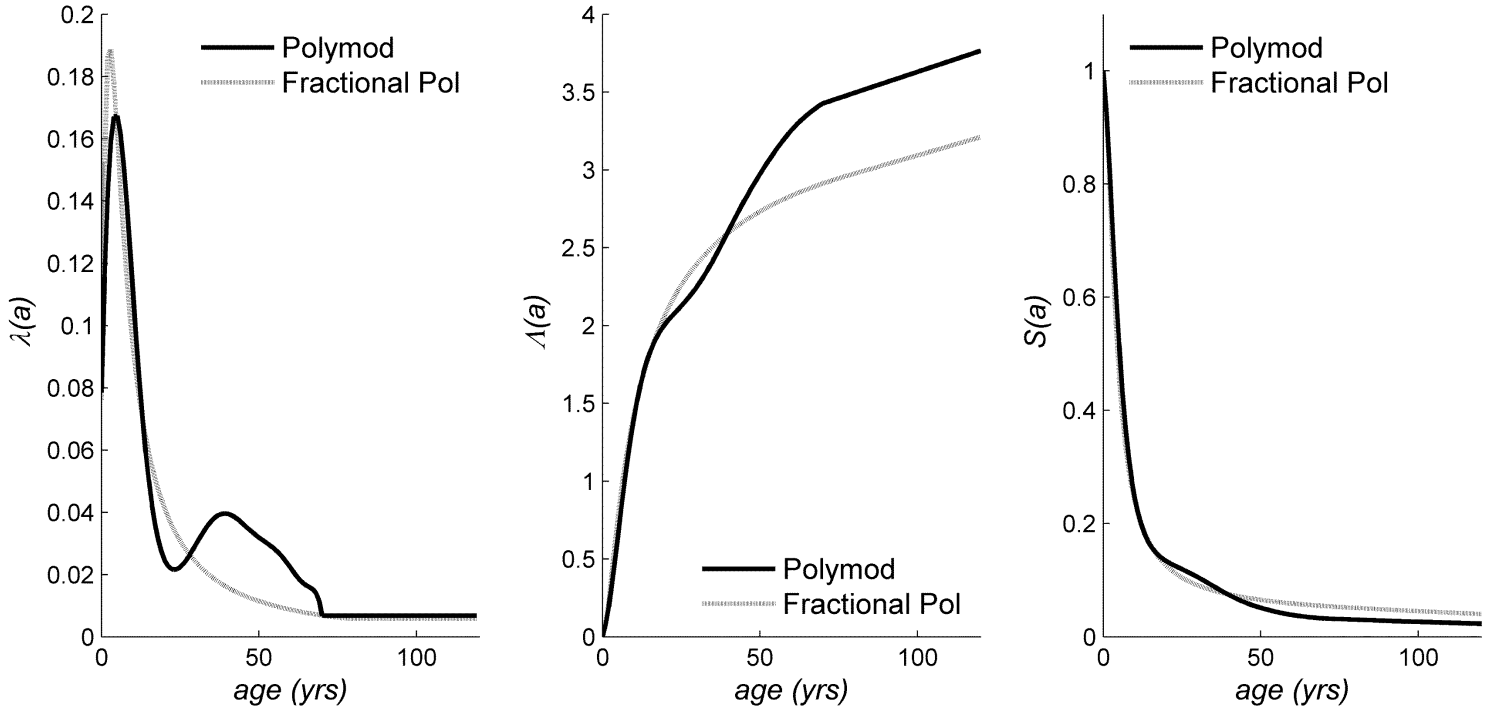
$$P(a) = 1 - e^{-\int_0^a \lambda(s)\,ds}$$

However, the FOI function λ has to be fitted to seroprevalence data by statistical methods and there are several ways of doing this...

There are two different recent estimates of the FOI of Varicella in Italy, based on Nardone et al (2007) (ESEN2...)

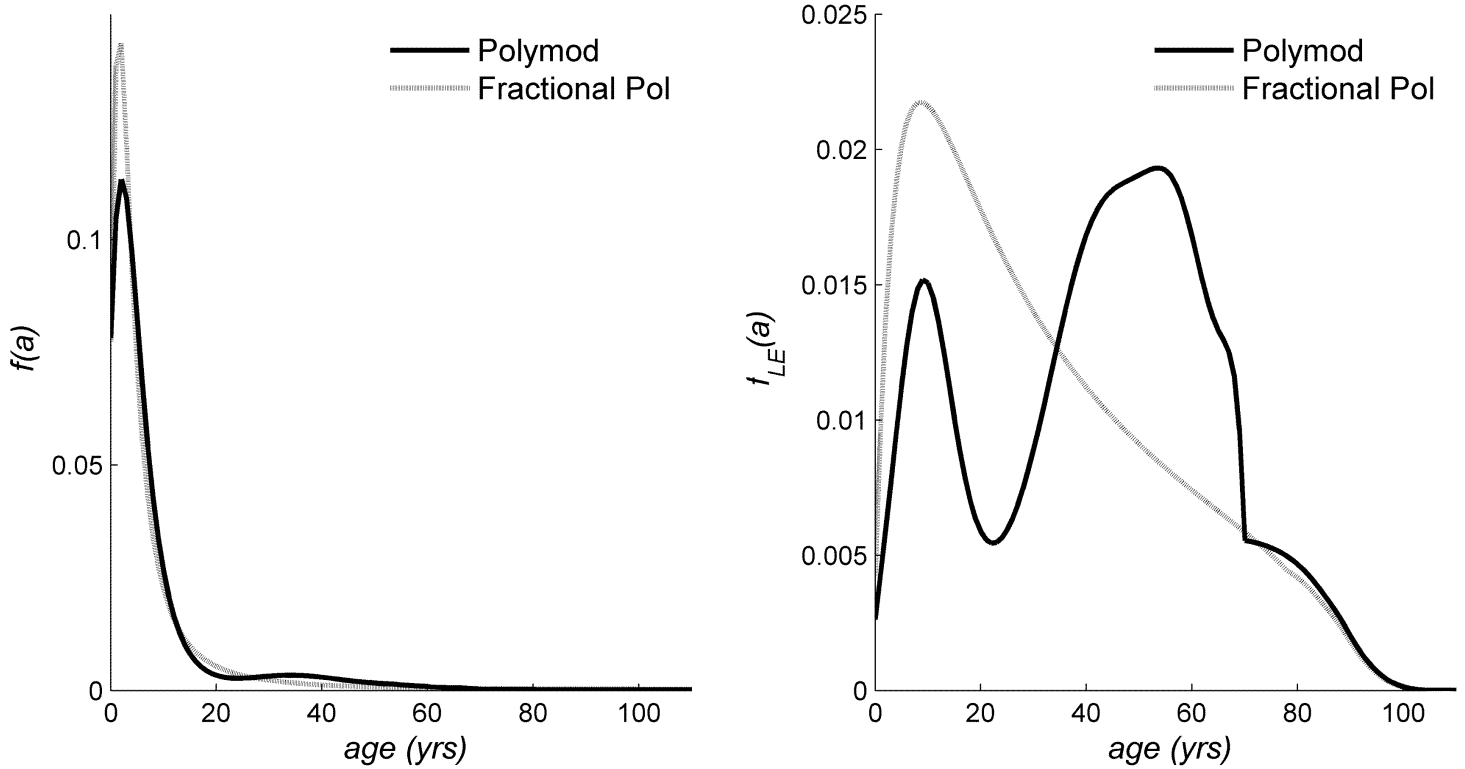
The first estimate is obtained (Del Fava 2012) by directly fitting to serological data a fractional polynomial model for the age-specific prevalence of previous infection (= 1 - survival...).

The second estimate is obtained (Del Fava 2012) by fitting the serological data with an age-structured SIR model (in endemic equilibrium) based on “Polymod” contact matrices (Mossong et al 2008).



(From the left: FOI, cumulative FOI, survival function)

The difference becomes more striking when looking at densities for the ages at first and last exposure:



Readings....

Giesecke: Modern infectious disease epidemiology (2nd ed., but 3rd is coming)

Krämer, Kretzschmar, Krickeberg: Modern infectious disease epidemiology

Diekmann, Heesterbeek, Britton: Mathematical tools for understanding infectious disease dynamics